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(54) **Use of an astrocyte function-improving agent for treating parkinson's disease**

Verwendung eines Mittels zur Verbesserung der Astrozytenfunktion zur Behandlung von Parkinsons Krankheit

Utilisation d' un agent améliorant la fonction des astrocytes pour le traitement de la maladie de Parkinson

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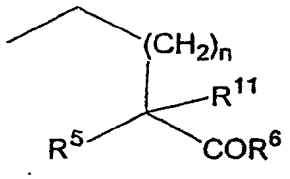
Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0001] The present invention relates to remedies for Parkinson's disease.

[0002] More particularly, the present invention relates to the use of a compound represented by formula (I), a non-toxic salt thereof, or a hydrate thereof, for the manufacture of a medicament for the prevention and/or treatment of Parkinson's disease or Parkinson's syndrome:



(I)

wherein the meaning of each symbol will be defined hereinafter.

2. Discussion of the Background

[0003] Parkinson's disease is a neurodegenerative disease which has been designated as one of specialization diseases by the Ministry of Health and Welfare in Japan. Concerning the clinical symptoms of Parkinson's disease, there are observed three large characteristics, i.e., 1) tremor, 2) akinesia and 3) rigtidity. Since it was found that the dopamine content was reduced in the brain of patients with Parkinson's disease, it is considered that a decrease in dopamine in the brain causes Parkinson's disease. Therefore, the treatment of Parkinson's disease is carried out by administering dopamine with a form of precursor, regulating the dopamine metabolism or using dopamine agonist.

[0004] There have been known several remedies for Parkinson's disease, and typical examples include L-dopa (dopamine precursor), dopamaine agonists , anticholinergic drugs, dopamine release promoters (amantadine *etc.*) and monoamine oxidase B inhibitors (selegiline *etc.*). However, these drugs suffer from some problems, such as a decline of the drug effect after prolonged administration, side effects, a failure to prevent the progress of the disease and the like, and thus therapeutic benefit obtained with antiparkinsonian drugs available at present is insufficient.

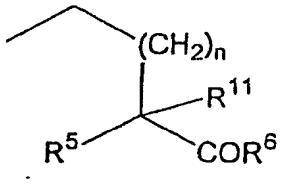
[0005] Parkinson's syndrome means a group of nervous diseases including Parkinson's disease which exhibit conditions similar to Parkinson's disease (i.e., the three symptoms as described above).

[0006] On the other hand, it is stated in JP-A-7-316092 (the term "JP-A" as used herein means an "unexamined published Japanese patent application") that compounds represented by formula (I) have effects of improving brain functions (in particular, astrocyte function) and therefore are useful in treating and preventing Alzheimer's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, olivopontocerebellar atrophy, neuronal dysfunction by stroke or traumatic injury, multiple sclerosis, astrocytoma, meningitis, brain abscess, Creutzfeldt-Jakob disease, AIDS dementia *etc.*

SUMMARY OF THE INVENTION

[0007] An object of the present invention is to provide an agent for Parkinson's disease.

[0008] This and other objects of the present invention have been attained bv the use of a compound represented by formula (I), a non-toxic salt thereof, or a hydrate thereof, for the manufacture of a medicament for the prevention and/or treatment of Parkinson's disease or Parkinson's syndrome:

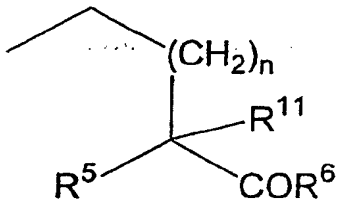


(I)

wherein the meaning of each symbol will be defined hereinafter.

DETAILED DESCRIPTION OF THE INVENTION

[0009] According to the present invention a compound is used represented by formula (I), a non-toxic salt thereof, or a hydrate thereof:



(I)

wherein R^6 represents hydroxy, C1-4 alkoxy, C1-4 alkoxy substituted with one phenyl, or $-NR^9R^{10}$,
wherein R^9 and R^{10} each independently represent:

(i) hydrogen,
(ii) C1-4 alkyl,
(iii) phenyl,
(iv) phenyl substituted with C1-4 alkoxy or carboxyl,
(v) a 4- to 7-membered heterocyclic ring containing one nitrogen atom, or
(vi) C1-4 alkyl substituted with phenyl,
C1-4 alkyl substituted with C1-4 alkoxy- or carboxyl-substituted phenyl,
C1-4 alkyl substituted with a 4- to 7-membered heterocyclic ring containing one nitrogen atom,
(vii) a 4- to 7-membered heterocyclic ring having 1 or 2 nitrogen atoms or a 4- to 7-membered heterocyclic ring having one nitrogen atom and one oxygen atom, together with the nitrogen atom to which they are bonded,
(viii) an amino acid residue together with the nitrogen atom to which they are bonded;

(1)n is 1;
R^{11} represents hydrogen; and
R^5 represents (C1-10 alkyl in which one of the carbon atom(s) is substituted with 1 to 3 fluorine atoms)-CH_2-,
with the proviso that R^5 does not represent F-$(CH_2)_5$-, F-$(CH_2)_6$-, F-$(CH_2)_7$- and F_3C-$(CH_2)_2$-; or
(2) n is 0 or 1;
R^{11} represents hydrogen or chlorine; and
R^5 represents:

C3-10 alkyl,
C3-10 alkenyl,
C2-10 alkoxy,
C2-10 alkylthio,
C3-7 cycloalkyl,
phenyl,
phenoxy,
F-$(CH_2)_m$, in which m is an integer of 5 to 7,
F_3C-$(CH_2)_2$-,

(C2-10 alkyl substituted with 1 or 2 chlorine atoms)-CH_2, or
(C1-5 alkyl substituted with 1 or 2 substituents selected from the group consisting of C1-4 alkoxy, C3-7 cycloalkyl, phenyl and phenoxy)-CH_2-; or
R^5 and R^{11}, taken together, form C3-10 alkylidene.

[0010] JP-A-7-316092 discloses that the compounds represented by formula (I) have an effect of improving astrocyte function and thus are effective for Alzheimer's disease *etc.* However, there is not described that these compounds are effective for Parkinson's disease and Parkinson's syndrome. Although the presence of reactive astrocytes was confirmed in Parkinson's disease (*Greenfield's Neuropathology*, 6th edition, Graham DL, Lantos PL (eds), Arnold, London, 1997), it has not been decided so far either these reactive astrocytes causes Parkinson's disease or are formed as the result thereof. It has been confirmed for the first time by the present invention that the compounds represented by formula (I) are effective in an experiment *in vivo* (Parkinson's disease model).

[0011] In a preferred embodiment, according to the present invention a compound is used of the formula (I) wherein n is 1, R11 is hydrogen, R5 is C3-10 alkyl and R6 is hydroxy and non-toxic salts thereof.

[0012] In a more preferred embodiment, according to the present invention (R)-2-propyloctanoic acid and non-toxic salts thereof are used. However, it is fully expected that not only (R)-2-propyloctanoic acid, which is a typical example of the compounds to be used according to the present invention, but any compounds represented by formula (I) are effective for Parkinson's disease because they have the effect of improving the astrocyte function.

[0013] The compounds represented by formula (1) are publicly known *per se* or can be produced by the method described in JP-A-7-316092 or PCT00/48982.

[0014] The compounds for use in the present invention can be converted into the corresponding salts by publicly known methods. Non-toxic and water-soluble salts are preferred. Examples of suitable salts include salts of alkali metals (potassium, sodium *etc.*), salts of alkaline earth metals (calcium, magnesium *etc.*) and salts of pharmaceutically acceptable amines (tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)amine, lysine, arginine, N-methyl-D-glucamine *etc.*). The sodium salts are particularly preferred.

[0015] The compounds to be used in the present invention can be converted into the corresponding acid addition salts by publicly known methods. Non-toxic and water-soluble acid addition salts are favorable. Examples of appropriate acid addition salts include inorganic acid salts such as hydrochlorides, hydrobromides, hydroiodides, sulfates, phosphates and nitrates, and organic acid salts such as acetates, lactates, tartarates, oxalates, fumarates, maleates, citrates, benzoates, methanesulfonates, ethanesulfonates, benzenesulfonates, toluenesulfonates, isethionates, glucuronates and gluconates.

[0016] The compounds to be used according to the present invention or salts thereof can be converted into hydrates by publicly known methods.

Pharmacological activity:

[0017] Because of having an effect of improving the astrocyte function, the compounds to be used according to the present invention represented by formula (I) are efficacious in a Parkinson's disease model as will be described hereinafter. Thus, it is expected that these compounds are effective for Parkinson's disease and Parkinson's syndrome.

Toxicity:

[0018] It has been confirmed that the compounds to be used according to the present invention represented by formula (I) have such low toxicity as being sufficiently safe in using as drugs. When (R)-2-propyloctanoic acid was intravenously administered to dogs in a single dose of 100 mg/kg, for example, no case of death was observed.

Application to drugs:

[0019] The compounds represented by formula (I) for use in the present invention, salts thereof or hydrates of the same, are useful in treating and/or preventing Parkinson's disease or Parkinson's syndrome.

[0020] For the purpose described above, the compounds represented by formula (I), a salt thereof, or a hydrate thereof may be normally administered to human or animal systemically or locally and orally or parenterally.

[0021] The doses to be administered are determined depending upon age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment *etc.* In the human adult, the doses per person per dose are generally between 1 mg and 1000 mg, by oral administration, up to several times per day, and between 0.1 mg and 100 mg, by subcutaneous, intravenous or intranasal administration up to several times per day, or by continuous administration between 1 and 24 hours per day into vein.

[0022] As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

[0023] The compounds to be used according to the present invention may be administered as inner solid compositions or inner liquid compositions for oral administration, or as injections, liniments or suppositories *etc.* for parenteral administration.

[0024] Inner solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders and granules *etc.* Furthermore, they also include gargling agents and sublingual agents for intraoral insertion and adsorption. Capsules contain hard capsules and soft capsules.

[0025] In such inner solid compositions, one or more of the active compound(s) are prepared as pharmaceuticals by known methods as they are, or by mixing with an inert diluent (lactose, mannitol, glucose, microcrystalline cellulose, starch *etc.*), connecting agents (hydroxypropyl cellulose, polyvinylpyrrolidone, magnesium metasilicate aluminate *etc.*), disintegrating agents (cellulose calcium glycolate *etc.*), lubricating agents (magnesium stearate *etc.*), stabilizing agents, assisting agents for dissolving (glutamic acid, asparaginic acid *etc.*) *etc.* If necessary, the pharmaceuticals may be coated with a coating agent (sugar, gelatin, hydroxypropyl cellulose, hydroxypropyl cellulose phthalate *etc.*), or be coated with two or more films. Furthermore, capsules of absorbable materials such as gelatin are also included.

[0026] Inner liquid compositions for oral administration include pharmaceutically acceptable water agents, suspensions, emulsions, syrups, elixirs *etc.* In such liquid compositions, one or more of the active compound(s) are dissolved, suspended or emulsified in inert diluent(s) generally used (purified water, ethanol, mixture thereof *etc.*). Furthermore, the liquid compositions may also contain wetting agents, suspending agents, emulsifying agents, sweetening agents, flavouring agents, perfuming agents, preserving agents, buffer agents *etc.*

[0027] Injections for parenteral administration include solutions, suspensions, emulsions, and solid injections which are dissolved or suspended in solvent(s) when they are used. One or more active compound(s) are dissolved, suspended or emulsified in solvent(s) when such compositions are used. Examples of the solvents include distilled water for injection and physiological salt solution, plant oil, propylene glycol, polyethylene glycol and alcohol such as ethanol *etc.*, and mixture thereof. Such compositions may contain stabilizing agent, assisting agents for dissolving (glutamic acid, asparaginic acid, POLYSOLBATE80 (registered trade mark) *etc.*), suspending agents, emulsifying agents, dispersing agents, buffer agents, preserving agents *etc.* They are manufactured and prepared by sterilization at the final step or aseptic treatment. They may also be manufactured in the form of sterile solid compositions, such as freeze-drying products, and they can be dissolved in sterilized or sterile distilled water for injection or other solvent before use.

[0028] Now, the present invention will be described in greater detail by reference to the following Examples. However, it is to be understood that the present invention is not construed as being limited thereto.

Example 1

Improvement effect of the compound to be used according to the present invention in the experimental model of Parkinson's disease induced by administration of MPTP:

[0029] Male C57BL/6 mice (body weight: 20 to 28 g) were divided into groups each having 6 to 12 animals. Without anesthetizing, MPTP (10 mg/kg; 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride) was intraperitoneally administered to the mice 4 times at intervals of 1 hour (*Brain Res., 824:* 224-231 (1999)). To the models thus prepared, Compound A of the present invention ((R)-2-propyloctanoic acid) was administered after 1, 6, 24 and 48 hours. Three days after the final administration, striata of the mice were collected. After weighing, the striata were immediately frozen and stored. Then, dopamine content and DOPAC (3,4-dihydroxypyenylacetate) content were measured by HPLC in a conventional manner and evaluated. Table 1 shows the result.

[0030] Dunnett's multiple comparison test (both sides) was performed on the basis of the data of the group with the administration of MPTP alone.

[0031] The values in Table 1 are shown by the average ± the standard deviation.

Table 1

	Dopamine content(μg/g)	DOPAC content (μg/g)
Control (physiological saline)	13.32 ± 2.34**	2.50 ± 0.38**
Compound A of invention 30 mg/kg	12.17 ± 1.41**	2.97 ± 0.49**
MPTP	2.96 ± 2.07	1.40 ± 0.78
MPTP + compound A of invention 3 mg/kg	4.13 ± 1.48	1.30 ± 0.31
MPTP + compound A of invention 10 mg/kg	5.45 ± 2.00*	2.07 ± 0.77
MPTP + compound A of invention 30 mg/kg	6.75 ± 2.72**	2.26 ± 0.52*

*: $p<0.05$, **: $p<0.01$

[0032] Compared with the group of the administration of MPTP alone, the groups of the administration of MPTP + the compound to be used according to the present invention showed significantly increased dopamine and DOPAC content depending on the dose. The data of the group with the compound to be used according to the present invention alone were almost the same as the data of the control group, which indicates that it showed no adverse effect when used alone in normal animals.

[0033] Also, the compounds to be used according to the present invention are efficacious even in post treatment administration, which makes them epoch-making drugs different from the existing ones.

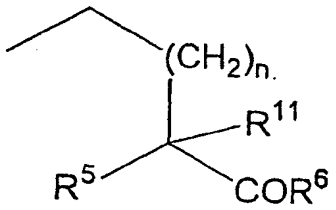
Formulation Example 1

Preparation of capsules:

[0034] (R)-2-propyloctanoic acid (1 g) was encapsulated into gelatin capsules to obtain 10 capsules each containing 100 mg of the active ingredient.

Claims

1. Use of a compound represented by formula (I), a non-toxic salt thereof, or a hydrate thereof, for the manufacture of a medicament for the prevention and/or treatment of Parkinson's disease or Parkinson's syndrome:



(I)

wherein R^6 represents hydroxy, C1-4 alkoxy, C1-4 alkoxy substituted with one phenyl or $-NR^9R^{10}$, wherein R^9 and R^{10} each independently represent:

(i) hydrogen,
(ii) C1-4 alkyl,
(iii) phenyl,
(iv) phenyl substituted with C1-4 alkoxy or carboxyl,
(v) a 4- to 7-membered heterocyclic ring containing one nitrogen atom, or
(vi) C1-4 alkyl substituted with phenyl,

C1-4 alkyl substituted with C1-4 alkoxy- or carboxyl substituted phenyl,
C1-4 alkyl substituted with a 4- to 7-membered heterocyclic ring containing one nitrogen atom,
(vii) a 4- to 7-membered heterocyclic ring having 1 or 2 nitrogen atoms or one nitrogen atom and one oxygen atom, together with the nitrogen atom to which they are bonded,
(viii) an amino acid residue together with the nitrogen atom to which they are bonded;
(1)n is 1;
R^{11} represents hydrogen; and
R^5 represents (C1-10 alkyl in which one of the carbon atom(s) is substituted with 1 to 3 fluorine atoms)-CH_2-, with the proviso that R^5 does not represent F-$(CH_2)_5$-, F-$(CH_2)_6$-, F-$(CH_2)_7$- and F_3C-$(CH_2)_2$-; or
(2) n is 0 or 1;
R^{11} represents hydrogen or chlorine; and
R^5 represents:

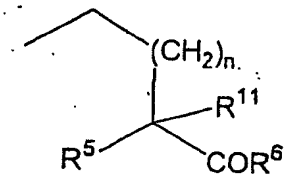
C3-10 alkyl,
C3-10 alkenyl,
C2-10 alkoxy,
C2-10 alkylthio,
C3-7 cycloalkyl,
phenyl,
phenoxy,
F-$(CH_2)_m$, in which m is an integer of 5 to 7,
F_3C-$(CH_2)_2$-,
(C2-10 alkyl substituted with 1 or 2 chlorine atoms)-CH_2, or
(C1-5 alkyl substituted with 1 or 2 substituents selected from the group consisting of C1-4 alkoxy, C3-7 cycloalkyl, phenyl and phenoxy)-CH_2-; or
R^5 and R^{11}, taken together, form C3-10 alkylidene.

2. The use according to claim 1 wherein said compound is a compound of the formula (I) wherein n is 1, R^{11} is hydrogen, R^5 is C3-10 alkyl and R^6 is hydroxy, non-toxic salts thereof or hydrate thereof.

3. The use according to claim 1 or 2 wherein said compound is (R)-2-propyloctanoic acid, a non-toxic salt thereof, or a hydrate thereof.

Patentansprüche

1. Verwendung einer Verbindung der Formel (I), eines nichttoxischen Salzes derselben oder eines Hydrats derselben zur Herstellung eines Medikaments zur Prävention und/oder Behandlung von Parkinson-Krankheit oder Parkinson-Syndrom:



(I)

worin R^6 für Hydroxy, C1-4-Alkoxy, mit einem Phenyl substituiertes C1-4-Alkoxy oder -NR^9R^{10} steht, wobei R^9 und R^{10} jeweils unabhängig voneinander für:

(i) Wasserstoff,
(ii) C1-4-Alkyl,
(iii) Phenyl,
(iv) Phenyl, das mit C1-4-Alkoxy oder Carboxyl substituiert ist,
(v) einen 4- bis 7-gliedrigen heterocyclischen Ring, der ein Stickstoffatom enthält, oder
(vi) mit Phenyl substituiertes C1-4-Alkyl,

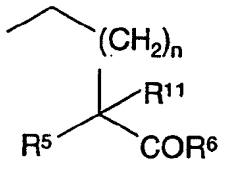
mit mit C1-4-Alkoxy oder Carboxyl substituiertem Phenyl substituiertes C1-4-Alkyl,
mit einem 4- bis 7-gliedrigen heterocyclischen Ring, der ein Stickstoffatom enthält, substituiertes C1-4-Alkyl,
(vii) einen 4- bis 7-gliedrigen heterocyclischen Ring mit einem oder zwei Stickstoffatomen oder einem Stickstoffatom und einem Sauerstoffatom zusammen mit dem Stickstoffatom, an das sie gebunden sind,
(viii) einen Aminosäurerest zusammen mit dem Stickstoffatom, an das sie gebunden sind, stehen;
(1) n für 1 steht;
R^{11} für Wasserstoff steht und
R^5 für (C1-10-Alkyl, wobei eines der Kohlenstoffatome mit 1 bis 3 Fluoratomen substituiert ist) $-CH_2-$ steht,
mit der Maßgabe, dass R^5 nicht für $F-(CH_2)_5-$, $F-(CH_2)_6-$, $F-(CH_2)_7-$ und $(F_3C-CH_2)_2-$ steht; oder
(2) n für 0 oder 1 steht;
R^{11} für Wasserstoff oder Chlor steht; und
R^5 für
C3-10-Alkyl,
C3-10-Alkenyl,
C2-10-Alkoxy,
C2-10-Alkylthio,
C3-7-Cycloalkyl,
Phenyl,
Phenoxy,
$F-(CH_2)_m$, wobei m eine ganze Zahl von 5 bis 7 ist,
$F_3C-(CH_2)_2-$,
(C2-10-Alkyl, das mit 1 oder 2 Chloratomen substituiert ist)$-CH_2$ oder
(C1-5-Alkyl, das mit 1 oder 2 Substituenten substituiert ist, die aus der Gruppe von C1-4-Alkoxy, C3-7-Cycloalkyl, Phenyl und
Phenoxy ausgewählt sind)$-CH_2-$ steht; oder R^5 und R^{11} zusammengenommen ein C3-10-Alkyliden bilden.

2. Verwendung nach Anspruch 1, wobei die Verbindung eine Verbindung der Formel (I), worin n 1 ist, R^{11} Wasserstoff ist, R^5 C3-10-Alkyl ist und R^6 Hydroxy ist, nichttoxische Salze derselben oder ein Hydrat derselben ist.

3. Verwendung nach Anspruch 1 oder 2, wobei die Verbindung (R)-2-Propyloctansäure, ein nichttoxisches Salz derselben oder ein Hydrat derselben ist.

Revendications

1. Utilisation d'un composé représenté par la formule (I), d'un sel non toxique de celui-ci ou d'un hydrate de celui pour la fabrication d'un médicament pour la prévention et/ou le traitement de la maladie de Parkinson ou du syndrome de Parkinson :



(I)

où R^6 représente hydroxy, C_{1-4} alcoxy, C_{1-4} alcoxy substitué avec un phényle ou $-NR^9R^{10}$,
où R^9 et R^{10} représentent chacun indépendamment :

(i) l'hydrogène,
(ii) C_{1-4} alkyle,
(iii) phényle,
(iv) phényle substitué avec C_{1-4} alcoxy ou carboxyle,
(v) un cycle hétérocyclique à 4 à 7 membres contenant un atome d'azote, ou
(vi) C_{1-4} alkyle substitué avec phényle,
C_{1-4} alkyle substitué avec phényle C_{1-4} alcoxy- ou carboxyl-substitué,

C_{1-4} alkyle substitué avec un cycle hétérocyclique à 4 à 7 membres contenant un atome d'azote,
(vii) un cycle hétérocyclique à 4 à 7 membres ayant 1 ou 2 atomes d'azote ou un atome d'azote et un atome d'oxygène, conjointement avec l'atome d'azote auquel ils sont liés,
(viii) un résidu d'aminoacide conjointement avec l'atome d'azote auquel ils sont liés ;
(1) n est 1 ;
R^{11} représente l'hydrogène ; et
R^5 représente (C_{1-10} alkyle dans lequel l'un des atomes de carbone est substitué avec 1 à 3 atomes de fluor)-CH_2-,
avec la condition que R^5 ne représente pas F-$(CH_2)_5$-, F-$(CH_2)_6$-, F-$(CH_2)_7$- et F_3C-$(CH_2)_2$- ; ou
(2) n est 0 ou 1 ;
R^{11} représente l'hydrogène ou le chlore ; et
R^5 représente :

C_{3-10} alkyle,
C_{3-10} alcényle,
C_{2-10} alcoxy,
C_{2-10} alkylthio,
C_{3-7} cycloalkyle,
phényle,
phénoxy,
F-$(CH_2)_m$, où m est un entier de 5 à 7,
F_3C-$(CH_2)_2$-,
(C_{2-10} alkyle substitué avec 1 ou 2 atomes de chlore)-CH_2, ou
(C_{1-5} alkyle substitué avec 1 ou 2 substituants choisis dans le groupe consistant en C_{1-4} alcoxy, C_{3-7} cycloalkyle, phényle et phénoxy)-CH_2- ; ou
R^5 et R^{11} pris ensemble forment C_{3-10} alkylidène.

2. Utilisation selon la revendication 1 où ledit composé est un composé de formule (I) où n est 1, R^{11} est l'hydrogène, R^5 est C_{3-10} alkyle et R^6 est hydroxy, ses sels non toxiques ou un hydrate de celui-ci.

3. Utilisation selon la revendication 1 ou 2 où ledit composé est l'acide (R)-2-propyloctanoïque, un sel non toxique de celui-ci ou un hydrate de celui-ci.